

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Vincent P. Stanton, Jr.                      Art Unit :  
Serial No. :    Examiner :  
Filed : HEREWITH  
Title : THYMIDYLATE SYNTHASE GENE SEQUENCE VARIANCES HAVING  
UTILITY IN DETERMINING THE TREATMENT OF DISEASE

Commissioner for Patents  
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Title:

Replace the title with the following new title:

-- THYMIDYLATE SYNTHASE GENE SEQUENCE VARIANCES HAVING  
UTILITY IN DETERMINING THE TREATMENT OF DISEASE--

In the specification:

Insert the enclosed Sequence Listing into the specification after the Oath and Declaration.

Replace the paragraph beginning at page 1, line 8, with the following new paragraph:

--This application is a divisional of U.S. Application Serial No. 09/658,659, filed  
September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June  
15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE  
METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE  
which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE  
SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING  
UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton,

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL624276315 US

I hereby certify under 37 CFR §1.10 that this correspondence is being  
deposited with the United States Postal Service as Express Mail Post  
Office to Addressee with sufficient postage on the date indicated below  
and is addressed to the Commissioner for Patents, Washington,  
D.C. 20231.

September 24, 2001  
Date of Deposit

[Signature]  
Signature

Lyba G Gray  
Typed or Printed Name of Person Signing Certificate

U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entireties including drawings and tables.--

Replace Table 10 beginning at page 171, with the following table:

**Table 10**

**Variance Table**

Hugo	GID	OMIM ID	VGX Symbol	Description
Variance Start	Variance			
U73338	U73338	156570	GEN-69	Methionine
Synthase (SEQ ID NO:1)				
	194	(-201)C>G		5'
	284	(-111)C>T		5'
	1136	742G>A	V248M	
	1252	858C>T	Silent	
	1334	940G>A	D314N	
	1699	1305T>C	Silent	
	3150	2756A>G	D919G	
	3207	2813G>T	S938I	
	3209	2815G>C	G939R	
	5444	5050C>A		3'
	5551	5157G>A		3'
	5573	5179C>T		3'
	5659	5265T>C		3'
	5678	5284T>C		3'
	5874	5480C>T		3'
	5934	5540A>G		3'
D78586	D78586	114010	GEN-BR	CAD PROTEIN (SEQ
ID NO:2)				
	3434	3408C>T	Silent	
	4313	4287T>C	Silent	
	4799	4773A>G	Silent	
	5255	5229C>T	Silent	
	5455	5429G>A	R1810Q	

Applicant : Vincent P. Stanton, Jr.  
Serial No. :  
Filed : HEREWITH  
Page : 3

Attorney's Docket No.: 11926-015002

5507	5481T>C	Silent
5810	5784C>T	Silent
6128	6102C>T	Silent
6626	6600C>T	Silent
6686	6660C>T	Silent

U09178 U09178 274270 GEN-HA  
Dihydropyrimidine Dehydrogenase (SEQ ID NO:3)

166	85T>C	C29R
577	496A>G	M166V
638	557A>G	Y186C
1708	1627A>G	I543V
3432	3351T>C	3'
3682	3601C>T	3'
3730	3649G>A	3'
3925	3844A>G	3'
3937	3856T>C	3'

U19720 U19720 600424 GEN-I1 Folate  
Transporter (SLC19A1) (SEQ ID NO:4)

175	80G>A	R27H
341	246C>G	Silent
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005^2006insG	3'
2582	2487T>G	3'
2617	2522C>T	3'
2652	2557T>C	3'

U92868 U92868 600424 GEN-LUK Homo sapiens reduced  
folate carrier (RFC1) gene, exons 1a, 1c and 1b (SEQ ID NO:5)

431	431A>G	Intron
441	441A>G	Intron
498	498C>T	Intron
579	579G>C	Intron
599	599G>C	Intron

X02308 X02308 188350 GEN-KL Thymidylate  
synthetase (SEQ ID NO:6)

1066	961T>C	3'
1136	1031A>G	3'
1497	1392T>A	3'

D00517 D00517 188350 GEN-LUC Thymidylate  
synthase, promoter (SEQ ID NO:7)

276	276C>T	Intron
321	321T>C	Intron
452	452G>A	Intron

104250 "E.E.E.3660"

457	457^insC	Intron
491	491C>A	Intron
533	533T>C	Intron
624	624A>C	Intron
639	639A>G	Intron
655	655T>C	Intron

D00596 D00596 188350 GEN-LUD Homo sapiens  
gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7,  
complete cds (SEQ ID NO:8)

701	701A>C	Intron
716	716A>G	Intron
732	732T>C	Intron
1293	1293A>G	Intron
1322	1322C>G	Intron
1379	1379T>C	Intron
1590	1590C>T	Intron
1688	1688C>G	Intron
2401	2401A>G	Intron
2429	2429G>A	Intron
2488	2488C>T	Intron
2594	2594G>T	Intron
2618	2618G>A	Intron
3083	3083G>A	Intron
3125	3125G>A	Intron
3212	3212C>T	Intron
3619	3619T>A	Intron
3635	3635G>A	Intron
4256	4256G>A	Intron
4898	4898A>G	Intron
5006	5006C>T	Intron
5062	5062G>A	Intron
5167	5167G>A	Intron
11069	11069A>G	Intron
11238	11238C>T	Intron
11293	11293T>G	Intron
11422	11422T>C	Intron
11686	11686C>T	Intron
12598	12598T>C	Intron
13171	13171T>C	Intron
13298	13298G>A	Intron
13645	13645T>C	Intron
13751	13751C>A	Intron
13782	13782T>C	Intron
13806	13806T>C	Intron
13813	13813T>C	Intron

104260 8666660

14479	14479A>G	Intron		
14546	14546^insT	Intron		
14585	14585C>T	Intron		
14729	14729G>A	Intron		
14787	14787C>T	Intron		
14795	14795G>A	Intron		
15041	15041T>C	Intron		
15343	15343G>A	Intron		
15449	15449G>A	Intron		
15502	15502G>A	Intron		
15545	15545C>T	Intron		
15589	15589A>G	Intron		
15769	15769C>T	3'		
15839	15839A>G	3'		
16148	16148G>A	3'		
16198	16198T>G	3'		
16202	16202G>T	Intron		
X59618	X59618	180390	GEN-M3	Ribonucleotide
reductase M2 polypeptide	(SEQ ID NO:9)			
128	(-67)G>A			5'
189	(-6)T>G			5'
524	330C>G			Silent
1399	1205T>A			3'
1464	1270G>A			3'
1636	1442C>T			3'
1738	1544C>T			3'
2259	2065T>C			3'
S72487	S72487	131222	GEN-3LD	Thymidine
phosphorylase, partial	(SEQ ID NO:10)			
183	19G>A			D7N
483	319C>T			3'
601	437G>C			3'
1299	1135G>A			3'
M58602	M58602	131222	GEN-LUB	Thymidine
phosphorylase, promoter and genomic	(SEQ ID NO:11)			
124	124C>T			3'
439	439G>A			3'
1044	1044^insCT			3'
1331	1331G>A			3'
1977	1977G>A			Intron
2149	2149G>A			Intron
2467	2467A>G			Intron
2634	2634C>G			Intron
2975	2975G>A			Intron
3116	3116G>T			Intron

3255	3255A>C	Intron
3344	3344T>C	Intron
4051	4051C>A	Intron
4782	4782G>A	Intron
5022	5022T>C	Intron
5266	5266G>A	Intron
5285	5285C>G	Intron
5438	5438T>A	Intron
5482	5482C>T	Intron
5629	5629G>A	Intron
5648	5648C>T	Intron
5731	5731G>A	Intron

M98045 M98045 136510 GEN-4C3 Homo sapiens  
folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)

802	732C>T	Silent
1747	1677G>T	3'
1900	1830T>C	3'

U24253 U24253 136510 GEN-LUE Human  
folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and  
partial cds (SEQ ID NO:13)

1424	1424C>A	Intron
1649	1649G>A	Intron
2554	2554A>G	Intron

U24252 U24252 136510 GEN-LUF  
Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID  
NO:14)

263	263A>G	Intron
266	266G>T	Intron
527	527C>G	Intron
1037	1037A>G	5'
1139	1139G>A	Intron
1217	1217C>T	Intron
1647	1647C>T	Intron
1955	1955G>A	Intron
2017	2017G>A	Intron
2037	2037G>A	Intron
2189	2189A>G	Intron
2282	2282C>T	Intron
2309	2309A>G	Intron

U09806 U09806 236250 GEN-4FZ Human  
methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID  
NO:15)

120	120T>C	Silent
464	464T>G	M155R
519	519C>T	Silent

11926-015002-6

668	668C>T	A223V
1059	1059T>C	Silent
1289	1289C>A	3'
1308	1308T>C	3'
1784	1784G>A	3'
AF061655	AF061655	123920
deaminase, promoter (SEQ ID NO:16)		GEN-LUJ
575	575T>C	Intron
648	648T>C	Intron
771	771G>C	Intron
883	883G>A	Intron
941	941^insC	5'
1051	1051A>C	K27Q

In the claims

Cancel claim 1-16.  
Add new claims 17 - 49

--17. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of:

- (a) nucleotide 1066 wherein N is C;
- (b) nucleotide 1136 wherein N is G;
- (c) nucleotide 1497 wherein N is A;

or the complement thereof.

18. The isolated nucleic acid probe of claim 17 comprising at least two of:

- (a) nucleotide 1066 wherein N is C;
- (b) nucleotide 1136 wherein N is G;
- (c) nucleotide 1497 wherein N is A;

or the complement thereof.

19. The probe of claim 17 comprising no more than 500 contiguous nucleotides of SEQ ID NO:6.

20. The probe of claim 17 comprising no more than 200 contiguous nucleotides of SEQ ID NO:6.

21. The probe of claim 17 comprising no more than 100 contiguous nucleotides of SEQ ID NO:6.

22. The probe of claim 17 comprising no more than 50 contiguous nucleotides of SEQ ID NO:6.

23. The probe of claim 17 comprising DNA.
24. The probe of claim 17 comprising a peptide nucleic acid.
25. The probe of claim 17 further comprising a detectable label.
26. The probe of claim 25 wherein the detectable label is a fluorescent label.
27. A method comprising:
- (a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;
  - (b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of:
    - (i) nucleotide 1066 wherein N is C;
    - (ii) nucleotide 1136 wherein N is G;
    - (iii) nucleotide 1497 wherein N is A;or the complement thereof; and
  - (c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.
28. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:7, the probe comprising at least one of:
- (a) nucleotide 276 wherein N is T;
  - (b) nucleotide 321 wherein N is C;
  - (c) nucleotide 452 wherein N is A;
  - (d) C is inserted after nucleotide 457;
  - (e) nucleotide 491 wherein N is A;
  - (f) nucleotide 533 wherein N is C;
  - (g) nucleotide 624 wherein N is C;
  - (h) nucleotide 639 wherein N is G;
  - (i) nucleotide 655 wherein N is C;
- or the complement thereof.
29. The isolated nucleic acid probe of claim 28 comprising at least two of:
- (a) nucleotide 276 wherein N is T;
  - (b) nucleotide 321 wherein N is C;
  - (c) nucleotide 452 wherein N is A;
  - (d) C is inserted after nucleotide 457;
  - (e) nucleotide 491 wherein N is A;
  - (f) nucleotide 533 wherein N is C;
  - (g) nucleotide 624 wherein N is C;
  - (h) nucleotide 639 wherein N is G;
  - (i) nucleotide 655 wherein N is C;



or the complement thereof.

30. The probe of claim 28 comprising no more than 500 contiguous nucleotides of

31. The probe of claim 28 comprising no more than 200 contiguous nucleotides of

32. The probe of claim 28 comprising no more than 100 contiguous nucleotides of

33. The probe of claim 28 comprising no more than 50 contiguous nucleotides of

34. The probe of claim 28 comprising DNA.

35. The probe of claim 28 comprising a peptide nucleic acid.

36. The probe of claim 28 further comprising a detectable label.

37. The probe of claim 36 wherein the detectable label is a fluorescent label.

38. A method comprising:

(a) providing a sample comprising nucleic acid molecules present in a biological

(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides

(i) nucleotide 276 wherein N is T;

(ii) nucleotide 321 wherein N is C;

(iii) nucleotide 452 wherein N is A;

(iv) C is inserted after nucleotide 457;

(v) nucleotide 491 wherein N is A;

(vi) nucleotide 533 wherein N is C;

(vii) nucleotide 624 wherein N is C;

(viii) nucleotide 639 wherein N is G;

(ixi) nucleotide 655 wherein N is C;

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the

39. An isolated nucleic acid probe comprising at least 15 contiguous nucleotides of

(a) nucleotide 701 wherein N is C;

(b) nucleotide 716 wherein N is G;

- (c) nucleotide 732 wherein N is C;  
(d) nucleotide 1293 wherein N is G;  
(e) nucleotide 1322 wherein N is G;  
(f) nucleotide 1379 wherein N is C;  
(g) nucleotide 1590 wherein N is T;  
(h) nucleotide 1688 wherein N is G;  
(i) nucleotide 2401 wherein N is G;  
(j) nucleotide 2429 wherein N is A;  
(k) nucleotide 2488 wherein N is T;  
(l) nucleotide 2594 wherein N is T;  
(m) nucleotide 2618 wherein N is A;  
(n) nucleotide 3083 wherein N is A;  
(o) nucleotide 3125 wherein N is A;  
(p) nucleotide 3212 wherein N is T;  
(q) nucleotide 3619 wherein N is A;  
(r) nucleotide 3635 wherein N is A;  
(s) nucleotide 4256 wherein N is A;  
(t) nucleotide 4898 wherein N is G;  
(u) nucleotide 5006 wherein N is T;  
(v) nucleotide 5062 wherein N is A;  
(w) nucleotide 5167 wherein N is A;  
(x) nucleotide 11069 wherein N is G;  
(y) nucleotide 11238 wherein N is T;  
(z) nucleotide 11293 wherein N is G;  
(aa) nucleotide 11422 wherein N is C;  
(bb) nucleotide 11686 wherein N is T;  
(cc) nucleotide 12598 wherein N is C;  
(dd) nucleotide 13171 wherein N is C;  
(ee) nucleotide 13298 wherein N is A;  
(ff) nucleotide 13645 wherein N is C;  
(gg) nucleotide 13751 wherein N is A;  
(hh) nucleotide 13782 wherein N is C;  
(ii) nucleotide 13806 wherein N is C;  
(jj) nucleotide 13813 wherein N is C;  
(kk) nucleotide 14479 wherein N is G;  
(ll) T is inserted after nucleotide 14546;  
(mm) nucleotide 14585 wherein N is T;  
(nn) nucleotide 14729 wherein N is A;  
(oo) nucleotide 14787 wherein N is T;  
(pp) nucleotide 14795 wherein N is A;  
(qq) nucleotide 15041 wherein N is C;  
(rr) nucleotide 15343 wherein N is A;  
(ss) nucleotide 15449 wherein N is A;  
(tt) nucleotide 15502 wherein N is A;

- or the complement thereof.

40. The isolated nucleic acid probe of claim 39 comprising at least two of:
- (a) nucleotide 701 wherein N is C;
  - (b) nucleotide 716 wherein N is G;
  - (c) nucleotide 732 wherein N is C;
  - (d) nucleotide 1293 wherein N is G;
  - (e) nucleotide 1322 wherein N is G;
  - (f) nucleotide 1379 wherein N is C;
  - (g) nucleotide 1590 wherein N is T;
  - (h) nucleotide 1688 wherein N is G;
  - (i) nucleotide 2401 wherein N is G;
  - (j) nucleotide 2429 wherein N is A;
  - (k) nucleotide 2488 wherein N is T;
  - (l) nucleotide 2594 wherein N is T;
  - (m) nucleotide 2618 wherein N is A;
  - (n) nucleotide 3083 wherein N is A;
  - (o) nucleotide 3125 wherein N is A;
  - (p) nucleotide 3212 wherein N is T;
  - (q) nucleotide 3619 wherein N is A;
  - (r) nucleotide 3635 wherein N is A;
  - (s) nucleotide 4256 wherein N is A;
  - (t) nucleotide 4898 wherein N is G;
  - (u) nucleotide 5006 wherein N is T;
  - (v) nucleotide 5062 wherein N is A;
  - (w) nucleotide 5167 wherein N is A;
  - (x) nucleotide 11069 wherein N is G;
  - (y) nucleotide 11238 wherein N is T;
  - (z) nucleotide 11293 wherein N is G;
  - (aa) nucleotide 11422 wherein N is C;
  - (bb) nucleotide 11686 wherein N is T;
  - (cc) nucleotide 12598 wherein N is C;
  - (dd) nucleotide 13171 wherein N is C;
  - (ee) nucleotide 13298 wherein N is A;
  - (ff) nucleotide 13645 wherein N is C;
  - (gg) nucleotide 13751 wherein N is A;
  - (hh) nucleotide 13782 wherein N is C;

- (ii) nucleotide 13806 wherein N is C;
- (jj) nucleotide 13813 wherein N is C;
- (kk) nucleotide 14479 wherein N is G;
- (ll) T is inserted after nucleotide 14546;
- (mm) nucleotide 14585 wherein N is T;
- (nn) nucleotide 14729 wherein N is A;
- (oo) nucleotide 14787 wherein N is T;
- (pp) nucleotide 14795 wherein N is A;
- (qq) nucleotide 15041 wherein N is C;
- (rr) nucleotide 15343 wherein N is A;
- (ss) nucleotide 15449 wherein N is A;
- (tt) nucleotide 15502 wherein N is A;
- (uu) nucleotide 15545 wherein N is T;
- (vv) nucleotide 15589 wherein N is G;
- (ww) nucleotide 15769 wherein N is T;
- (xx) nucleotide 15839 wherein N is G;
- (yy) nucleotide 16148 wherein N is A;
- (zz) nucleotide 16198 wherein N is G; and
- (aaa) nucleotide 16202 wherein N is T;

or the complement thereof.

41. The probe of claim 39 comprising no more than 500 contiguous nucleotides of SEQ ID NO:8.

42. The probe of claim 39 comprising no more than 200 contiguous nucleotides of SEQ ID NO:8.

43. The probe of claim 39 comprising no more than 100 contiguous nucleotides of SEQ ID NO:8.

44. The probe of claim 39 comprising no more than 50 contiguous nucleotides of SEQ ID NO:8.

45. The probe of claim 39 comprising DNA.

46. The probe of claim 39 comprising a peptide nucleic acid.

47. The probe of claim 39 further comprising a detectable label.

48. The probe of claim 47 wherein the detectable label is a fluorescent label.

49. A method comprising:

(a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient;

(b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:8, the probe comprising at least one of:

- (i) nucleotide 701 wherein N is C;
- (ii) nucleotide 716 wherein N is G;
- (iii) nucleotide 732 wherein N is C;
- (iv) nucleotide 1293 wherein N is G;
- (v) nucleotide 1322 wherein N is G;
- (vi) nucleotide 1379 wherein N is C;
- (vii) nucleotide 1590 wherein N is T;
- (viii) nucleotide 1688 wherein N is G;
- (ix) nucleotide 2401 wherein N is G;
- (x) nucleotide 2429 wherein N is A;
- (xi) nucleotide 2488 wherein N is T;
- (xii) nucleotide 2594 wherein N is T;
- (xiii) nucleotide 2618 wherein N is A;
- (xiv) nucleotide 3083 wherein N is A;
- (xv) nucleotide 3125 wherein N is A;
- (xvi) nucleotide 3212 wherein N is T;
- (xvii) nucleotide 3619 wherein N is A;
- (xviii) nucleotide 3635 wherein N is A;
- (xix) nucleotide 4256 wherein N is A;
- (xx) nucleotide 4898 wherein N is G;
- (xxi) nucleotide 5006 wherein N is T;
- (xxii) nucleotide 5062 wherein N is A;
- (xxiii) nucleotide 5167 wherein N is A;
- (xxiv) nucleotide 11069 wherein N is G;
- (xxv) nucleotide 11238 wherein N is T;
- (xxvi) nucleotide 11293 wherein N is G;
- (xxvii) nucleotide 11422 wherein N is C;
- (xxviii) nucleotide 11686 wherein N is T;
- (xxix) nucleotide 12598 wherein N is C;
- (xxx) nucleotide 13171 wherein N is C;
- (xxxi) nucleotide 13298 wherein N is A;
- (xxxii) nucleotide 13645 wherein N is C;
- (xxxiii) nucleotide 13751 wherein N is A;
- (xxxiv) nucleotide 13782 wherein N is C;
- (xxxv) nucleotide 13806 wherein N is C;
- (xxxvi) nucleotide 13813 wherein N is C;
- (xxxvii) nucleotide 14479 wherein N is G;
- (xxxviii) T is inserted after nucleotide 14546;
- (xxxix) nucleotide 14585 wherein N is T;
- (xl) nucleotide 14729 wherein N is A;
- (xli) nucleotide 14787 wherein N is T;
- (xlii) nucleotide 14795 wherein N is A;

104260 " 886660

- (xliii) nucleotide 15041 wherein N is C;
- (xliv) nucleotide 15343 wherein N is A;
- (xlv) nucleotide 15449 wherein N is A;
- (xlvi) nucleotide 15502 wherein N is A;
- (xlvii) nucleotide 15545 wherein N is T;
- (xlviii) nucleotide 15589 wherein N is G;
- (xlix) nucleotide 15769 wherein N is T;
- (l) nucleotide 15839 wherein N is G;
- (li) nucleotide 16148 wherein N is A;
- (lii) nucleotide 16198 wherein N is G; and
- (liii) nucleotide 16202 wherein N is T

or the complement thereof; and

(c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.--

FILED

REMARKS

The amendment to the specification is made solely to insert the Sequence Listing and SEQ ID NOS. into the specification. No new matter is introduced. The accompanying declaration by the inventor confirms that the sequences in the Sequence Listing are the same as those incorporated by reference into the original specification by providing the GenBank® Accession Number for each sequence. A signed declaration will be filed under separate cover.

Applicant requests that claims 17-49 be examined together without restriction. Each of SEQ ID NOS:6, 7, and 8 relate to the human thymidylate synthetase gene. SEQ ID NO:6 corresponds to the coding region. SEQ ID NO:7 corresponds to the promoter region. SEQ ID NO:9 corresponds to the exons. Three SEQ ID NOS are required even though only one gene is referenced because the original specification identified the sequences by providing three GenBank® Accession Numbers.

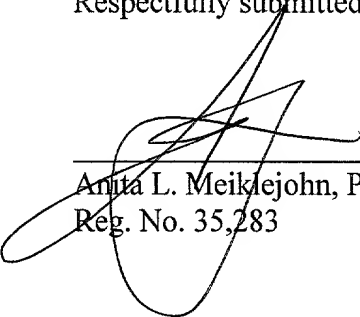
Each of the nucleotides specified in the claims represents a single nucleotide polymorphism in the human thymidylate synthetase gene.

Attached is a marked-up version of the changes being made by the current amendment.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 24 Sept 2001

  
Anita L. Meiklejohn, Ph.D.  
Reg. No. 35,283

Fish & Richardson P.C.  
225 Franklin Street  
Boston, MA 02110-2804  
Telephone: (617) 542-5070  
Facsimile: (617) 542-8906

20238832.doc

**Version with markings to show changes made**

**In the specification:**

The paragraph beginning at page 1, line 8, has been amended as follows:

This application is a divisional of U.S. Application Serial No. 09/658,659, filed September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June 15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entirety including drawings and tables.

Table 10 beginning at page 171 has been amended as follows:

**Table 10**

**Variance Table**

Hugo	GID	OMIM ID	VGX Symbol	Description
Variance Start		Variance		
U73338	U73338	156570	GEN-69	Methionine
Synthase (SEQ ID NO:1)				
	194	(-201)C>G		5'
	284	(-111)C>T		5'
	1136	742G>A		V248M
	1252	858C>T		Silent



1334	940G>A	D314N
1699	1305T>C	Silent
3150	2756A>G	D919G
3207	2813G>T	S938I
3209	2815G>C	G939R
5444	5050C>A	3'
5551	5157G>A	3'
5573	5179C>T	3'
5659	5265T>C	3'
5678	5284T>C	3'
5874	5480C>T	3'
5934	5540A>G	3'

D78586	D78586	114010	GEN-BR	CAD PROTEIN (SEQ
<u>ID NO:2)</u>				

3434	3408C>T	Silent
4313	4287T>C	Silent
4799	4773A>G	Silent
5255	5229C>T	Silent
5455	5429G>A	R1810Q
5507	5481T>C	Silent
5810	5784C>T	Silent
6128	6102C>T	Silent
6626	6600C>T	Silent
6686	6660C>T	Silent

U09178	U09178	274270	GEN-HA
<u>Dihydropyrimidine Dehydrogenase (SEQ ID NO:3)</u>			

166	85T>C	C29R
577	496A>G	M166V
638	557A>G	Y186C
1708	1627A>G	I543V
3432	3351T>C	3'
3682	3601C>T	3'
3730	3649G>A	3'
3925	3844A>G	3'
3937	3856T>C	3'

U19720	U19720	600424	GEN-I1	Folate
Transporter (SLC19A1)	<u>(SEQ ID NO:4)</u>			

175	80G>A	R27H
341	246C>G	Silent
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005^2006insG	3'
2582	2487T>G	3'

11926-015002

	2617		2522C>T	3'
	2652		2557T>C	3'
U92868	U92868	600424	GEN-LUK	Homo sapiens reduced
folate carrier (RFC1) gene, exons 1a, 1c and 1b (SEQ ID NO:5)				
	431		431A>G	Intron
	441		441A>G	Intron
	498		498C>T	Intron
	579		579G>C	Intron
	599		599G>C	Intron
X02308	X02308	188350	GEN-KL	Thymidylate
synthetase (SEQ ID NO:6)				
	1066		961T>C	3'
	1136		1031A>G	3'
	1497		1392T>A	3'
D00517	D00517	188350	GEN-LUC	Thymidylate
synthase, promoter (SEQ ID NO:7)				
	276		276C>T	Intron
	321		321T>C	Intron
	452		452G>A	Intron
	457		457^insC	Intron
	491		491C>A	Intron
	533		533T>C	Intron
	624		624A>C	Intron
	639		639A>G	Intron
	655		655T>C	Intron
D00596	D00596	188350	GEN-LUD	Homo sapiens
gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7,				
complete cds (SEQ ID NO:8)				
	701		701A>C	Intron
	716		716A>G	Intron
	732		732T>C	Intron
	1293		1293A>G	Intron
	1322		1322C>G	Intron
	1379		1379T>C	Intron
	1590		1590C>T	Intron
	1688		1688C>G	Intron
	2401		2401A>G	Intron
	2429		2429G>A	Intron
	2488		2488C>T	Intron
	2594		2594G>T	Intron
	2618		2618G>A	Intron
	3083		3083G>A	Intron
	3125		3125G>A	Intron
	3212		3212C>T	Intron
	3619		3619T>A	Intron



2259 2065T>C 3'  
S72487 S72487 131222 GEN-3LD Thymidine  
phosphorylase, partial (SEQ ID NO:10)  
183 19G>A D7N  
483 319C>T 3'  
601 437G>C 3'  
1299 1135G>A 3'  
M58602 M58602 131222 GEN-LUB Thymidine  
phosphorylase, promoter and genomic (SEQ ID NO:11)  
124 124C>T 3'  
439 439G>A 3'  
1044 1044^insCT 3'  
1331 1331G>A 3'  
1977 1977G>A Intron  
2149 2149G>A Intron  
2467 2467A>G Intron  
2634 2634C>G Intron  
2975 2975G>A Intron  
3116 3116G>T Intron  
3255 3255A>C Intron  
3344 3344T>C Intron  
4051 4051C>A Intron  
4782 4782G>A Intron  
5022 5022T>C Intron  
5266 5266G>A Intron  
5285 5285C>G Intron  
5438 5438T>A Intron  
5482 5482C>T Intron  
5629 5629G>A Intron  
5648 5648C>T Intron  
5731 5731G>A Intron  
M98045 M98045 136510 GEN-4C3 Homo sapiens  
folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)  
802 732C>T Silent  
1747 1677G>T 3'  
1900 1830T>C 3'  
U24253 U24253 136510 GEN-LUE Human  
folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and  
partial cds (SEQ ID NO:13)  
1424 1424C>A Intron  
1649 1649G>A Intron  
2554 2554A>G Intron  
U24252 U24252 136510 GEN-LUF  
Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID  
NO:14)

104250 663060

Serial No. :

Filed : HERewith

Page : 21

263	263A>G	Intron
266	266G>T	Intron
527	527C>G	Intron
1037	1037A>G	5'
1139	1139G>A	Intron
1217	1217C>T	Intron
1647	1647C>T	Intron
1955	1955G>A	Intron
2017	2017G>A	Intron
2037	2037G>A	Intron
2189	2189A>G	Intron
2282	2282C>T	Intron
2309	2309A>G	Intron

U09806 U09806 236250 GEN-4FZ Human  
methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID  
NO:15)

120	120T>C	Silent
464	464T>G	M155R
519	519C>T	Silent
668	668C>T	A223V
1059	1059T>C	Silent
1289	1289C>A	3'
1308	1308T>C	3'
1784	1784G>A	3'

AF061655 AF061655 123920 GEN-LUJ Cytidine  
deaminase, promoter (SEQ ID NO:16)

575	575T>C	Intron
648	648T>C	Intron
771	771G>C	Intron
883	883G>A	Intron
941	941^insC	5'
1051	1051A>C	K27Q